UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	CHOP-0019 / CHOP-0088U	1864

110 7590 07/23/2010

DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
07/23/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/20/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,24,28,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,24,28,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and response filed April 20, 2010 has been received and entered. Claims 3-23, 25-27, 29-42 have been canceled, while claim 1, 24 and 44 have been amended. Claims 1-2, 24, 28, 43 and 44 are pending and under consideration in the instant application.

Withdrawn- Objection to Specification

The objection to the disclosure is withdrawn in view of amendments to the specification.

Claim Rejections- 35 USC § 112 –Necessitated by amendments

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 24, 28, 43 and 44 were rejected under 35 U.S.C. 112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. The rejection set forth on pp. 2-7 of the previous office action dated January 20, 2010 is maintained for the reasons of record.

Applicants' amendments to the claims and arguments filed April 20, 2010 have been fully considered and found not persuasive.

The previous office action indicated an enabled scope for a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral vector, said method comprising (i) intramuscularly administering an effective amount of an rAAV to a mammal having genetic defect that shows symptoms of hemophilia B, and wherein said genetic defect can result in generation of inhibitory antibodies to factor IX upon administration of exogenous Factor IX, and (ii) intravenously or intraperitoneally administering to said mammal cyclophosphamide prior to or simultaneously with said adeno-associated viral vector delivery before formation of said inhibitory antibodies, thereby preventing the formation of inhibitory antibodies to Factor IX in said mammal, and wherein said rAAV

comprises a nucleic acid encoding Factor IX operably linked to an expression control element and the delivered Factor IX being from the same species as said mammal.

Applicants' amendment of base claim 1 to recite that the genetic defect is a large gene deletion in a gene encoding Factor IX does not obviate the grounds for rejection. It was indicated that the disclosure is not enabled for genetic defect other than one wherein mammal shows symptoms of hemophilia B resulting in generation of inhibitory antibodies to Factor IX.

Applicants argue that claims have been amended to recite that the particular defect is a large gene deletion in a gene encoding Factor IX, which is clearly supported by the examples of the instant specification. The mouse model used by Applicants "comprises a large deletion in the gene encoding F.IX" (see page 10, lines 16 - 17). Moreover, claim 1 has been amended to clarify that the generation of inhibitory antibodies results upon administration of exogenous Factor IX. Applicants assert that claim 24 has been amended to describe the effects of the large deletion in the gene encoding Factor IX, and recites that the large gene deletion results in no endogenous expression of Factor IX, while claim 44 has been amended to require intramuscular administration of the vector.

Applicants' arguments have been fully considered but are not persuasive. Applicants should note that the specification exemplifies the prevalence of inhibitor development in a murine model of hemophilia is caused by a large gene deletion affecting the promoter region and exons 1-3 of the F-IX gene resulting in an absence of F.IX transcript and protein (see page 13, lines 7-12). The issue is that the claims as amended read on mammal having large gene deletion of any size at any location (coding or non coding or complete) of Factor IX gene. The term "large deletion of Factor IX" embraces deletion in coding, non-coding or complete gene deletion resulting is no detectable endogenous expression of factor IX. The guidance provided in the specification is limited to deletion of exons 1-3 of the F-IX gene (see example). Prior to instant invention, Matthew et al (Journal of Clinical Investigation, 1987, 79, 746-753) reported DNA from nine hemophilia B patients who produce anti-factor IX inhibitors (antibodies). It is disclosed that two inhibitor patients showed total deletions of the factor IX gene, while other two showed two separate deletions of- 5.0 kb that removes exon e and 9 and 29 kb that removes exons g and h but leaves exon f intact. Matthew et al further reported that remaining five other inhibitor patients have a structurally intact factor IX gene suggesting that large structural factor

IX gene defects predispose hemophilia B patients to developing an anti-factor IX inhibitor, the development of an inhibitor can be associated with other defects of the factor IX gene (See abstract). The specification fails to provide an enabling disclosure for the breadth of the claimed invention because the specification fails to provide regions and portion of FIX gene that is deleted and capable of producing Factor IX antibodies upon administration of Factor IX. Absent of evidence to the contrary, it is not clear that if any large gene deletion of FIX in any mammal would be functional and capable of producing FIX antibodies in the same manner as they have been exemplified in prior art for a mouse whose genome comprises disruption in endogenous FIX gene such that no functional protein is made. Given, the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention without a reasonable expectation of success.

A direct recitation of mammal having genetic defect showing symptoms of hemophilia B and wherein said genetic defect can result in generation of inhibitory antibodies to factor IX upon administration of exogenous Factor IX, would obviate the basis of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 24, 28, 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "large" in claim 1 is a relative term which renders the claim indefinite. The term "large" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, it is unclear as to gene deletion of FIX is large relative to which polynucleotide sequence. Claims 2, 24, 28, 43 and 44 directly or indirectly depend on claim 1. Appropriate correction is required.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Smith et al (Gene Therapy (1996), 3(6), 496-502) and Dwarki et al (WO9906562).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
AU 1632

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632